METRONIDAZOLE- metronidazole injection, solution
Hospira, Inc.

METRONIDAZOLE

Injection, USP

500 mg (5 mg/mL)

Single Dose Container
Flexible Container

For Intravenous Infusion Only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole and other antibacterial drugs, metronidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats (see **PRECAUTIONS**). Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the **INDICATIONS AND USAGE** section below.

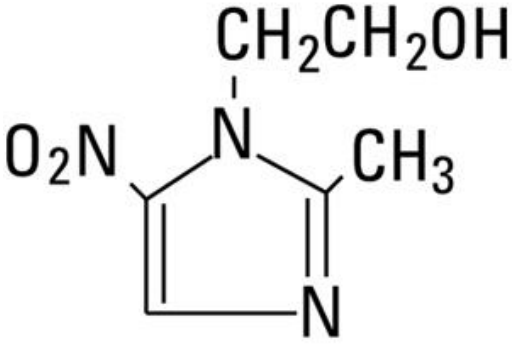
DESCRIPTION

Metronidazole Injection, USP is a sterile, nonpyrogenic, isotonic, buffered parenteral dosage form of metronidazole in water for injection.

Each 100 mL contains metronidazole 500 mg (5 mg/mL) and sodium chloride 790 mg in water for injection; with dibasic sodium phosphate (anhydrous) 48 mg and citric acid (anhydrous) 23 mg added as buffers. The osmolarity of this solution is 314 mOsmol/liter (calc.). Each 100 mL contains 14 mEq sodium, pH 5.8 (4.5 — 7.0).

Metronidazole is classified as a synthetic antibacterial and antiprotozoal agent and is administered by the intravenous route.

Metronidazole, USP is chemically designated 2-methyl-5-nitroimidazole-1-ethanol ($C_6H_9N_3O_3$), a crystalline powder sparingly soluble in water. It has the following structural formula:



Sodium Chloride, USP is chemically designated NaCl, a white crystalline powder freely

soluble in water.

Water for Injection, USP is chemically designated H_2O.

The flexible plastic container is fabricated from a specially formulated polyvinylchloride. Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of its chemical components in very small amounts before the expiration period is attained. However, the safety of the plastic has been confirmed by tests in animals according to USP biological standards for plastic containers.

CLINICAL PHARMACOLOGY

In patients treated with metronidazole injection using a dosage regimen of 15 mg/kg loading dose followed six hours later by 7.5 mg/kg every six hours, the average peak steady-state concentrations (C_{max}) and trough (C_{min}) were 25 mcg/mL and 18 mcg/mL, respectively. Plasma concentrations of metronidazole are proportional to the administered dose. An eight-hour intravenous infusion of 100 mg to 4,000 mg of metronidazole in normal subjects showed a linear relationship between dose and peak plasma concentration. The average elimination half-life of metronidazole in healthy subjects is eight hours.

Distribution

Metronidazole is the major component appearing in the plasma, with lesser quantities of metabolites also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Metronidazole appears in cerebrospinal fluid, saliva and breast milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Following a single intravenous dose of metronidazole 500 mg, 4 healthy subjects who underwent gastrointestinal endoscopy had peak gastric juice metronidazole concentrations of 5 to 6 mcg/mL at one hour post-dose. In patients receiving intravenous metronidazole in whom gastric secretions are continuously removed by nasogastric aspiration, sufficient metronidazole may be removed in the aspirate to cause a reduction in serum levels.

Metabolism

The metabolites of metronidazole result primarily from side-chain oxidation [1-(βhydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-ylacetic acid] and glucuronide conjugation. Both the parent compound and the hydroxyl metabolite possess *in vitro* antimicrobial activity.

Excretion

The major route of elimination of metronidazole and its metabolites is via the urine (60 to 80% of the dose), with approximately 20% of the amount excreted appearing as unchanged metronidazole. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m^2. Fecal excretion accounts for 6 to 15% of the dose.

Renal Impairment

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole.

Subjects with end-stage renal disease (ESRD; CL_{CR}= 8.1±9.1 mL/min) and who received a single intravenous infusion of metronidazole 500 mg had no significant change in metronidazole pharmacokinetics but had 2-fold higher C_{max} of hydroxy-metronidazole and 5-fold higher C_{max} of metronidazole acetate, compared to healthy subjects with normal renal function (CL_{CR}= 126 ± 16 mL/min). Thus, on account of the potential accumulation of metronidazole metabolites in ESRD patients, monitoring for metronidazole associated adverse events is recommended (see **PRECAUTIONS**).

Effect of Dialysis

Following a single intravenous infusion or oral dose of metronidazole 500 mg, the

clearance of metronidazole was investigated in ESRD subjects undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A hemodialysis session lasting for 4 to 8 hours removed 40% to 65% of the administered metronidazole dose, depending on the type of the dialyzer membrane used and the duration of the dialysis session. If the administration of metronidazole cannot be separated from the dialysis session, supplementation of metronidazole dose following hemodialysis should be considered (see **DOSAGE AND ADMINISTRATION**). A peritoneal dialysis session lasting for 7.5 hours removed approximately 10% of the administered metronidazole dose. No adjustment in metronidazole dose is needed in ESRD patients undergoing CAPD.

Hepatic Impairment

Following a single intravenous infusion of 500 mg metronidazole, the mean AUC_{24} of metronidazole was higher by 114% in patients with severe (Child-Pugh C) hepatic impairment, and by 54% and 53% in patients with a mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to healthy control subjects. There were no significant changes in the AUC_{24} of hydroxy-metronidazole in these hepatically impaired patients. A reduction in metronidazole dosage by 50% is recommended in patients with severe (Child-Pugh C) hepatic impairment (see **DOSAGE AND ADMINISTRATION**). No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Geriatric Patients

Following a single 500 mg oral or IV dose of metronidazole, subjects >70 years old with no apparent renal or hepatic dysfunction had a 40% to 80% higher mean AUC of hydroxy-metronidazole (active metabolite), with no apparent increase in the mean AUC of metronidazole (parent compound), compared to young healthy controls < 40 years old. In geriatric patients, monitoring for metronidazole associated adverse events is recommended (see **PRECAUTIONS**).

Pediatric Patients

In one study newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first three days of life, was inversely related to gestational age. In infants whose gestational ages were between 28 and 40 weeks, the corresponding elimination half-lives ranged from 109 to 22.5 hours.

Microbiology

Mechanism of Action

Metronidazole, a nitroimidazole, exerts antibacterial effects in an anaerobic environment against most obligate anaerobes. Once metronidazole enters the organism by passive diffusion and activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced; this process includes intra-cellular electron transport proteins such as ferredoxin, transfer of an electron to the nitro group of the metronidazole, and formation of a short-lived nitroso free radical. Because of this alteration of the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of bacteria. The precise mechanism of action of metronidazole is unclear.

Resistance

A potential for development of resistance exists against metronidazole.

Resistance may be due to multiple mechanisms that include decreased uptake of the drug, altered reduction efficiency, overexpression of the efflux pumps, inactivation of the drug, and/or increased DNA damage repair.

Metronidazole does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

Antimicrobial Activity

Metronidazole has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Gram-positive anaerobes

Clostridium species
Eubacterium species
Peptococcus species
Peptostreptococcus species

Gram-negative anaerobes

Bacteroides fragilis group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*)
Fusobacterium species

The following *in vitro* data are available, **but their clinical significance is unknown.**

Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of metronidazole in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-negative anaerobes

Bacteroides fragilis group (*B. caccae, B. uniformis*)
Prevotella species (*P. bivia, P. buccae, P. disiens*)

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

INDICATIONS AND USAGE

Treatment of Anaerobic Infections

Metronidazole Injection, USP is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to metronidazole.

Metronidazole is effective in *Bacteroides fragilis* infections resistant to clindamycin, chloramphenicol and penicillin.

Intra-abdominal Infections, including peritonitis, intra-abdominal abscess and liver abscess, caused by *Bacteroides* species including the *B. fragilis* group (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus*). *Clostridium* species, *Eubacterium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Skin and Skin Structure Infections caused by *Bacteroides* species including *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species and *Fusobacterium* species.

Gynecologic Infections, including endometritis, endomyometritis, tubo-ovarian abscess, and post-surgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species and *Fusobacterium* species.

Bacterial Septicemia caused by *Bacteroides* species including the *B. fragilis* group and *Clostridium* species.

Bone and Joint Infections, as adjunctive therapy, caused by *Bacteroides* species including the *B. fragilis* group.

Central Nervous System (CNS) Infections, including meningitis and brain abscess,

caused by *Bacteroides* species including the *B. fragilis* group.

Lower Respiratory Tract Infections, including pneumonia, empyema, and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.

Endocarditis caused by *Bacteroides* species including the *B. fragilis* group.

Prophylaxis

The prophylactic administration of Metronidazole Injection, USP preoperatively, intraoperatively, and postoperatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated.

Prophylactic use of Metronidazole Injection, USP should be discontinued within 12 hours after surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see **DOSAGE AND ADMINISTRATION**).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of metronidazole and other antibacterial drugs, metronidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Hypersensitivity

Metronidazole Injection, USP is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

Psychotic Reaction with Disulfiram

Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently. Do not administer metronidazole to patients who have taken disulfiram within the last two weeks (see **PRECAUTIONS-Drug Interactions**).

Interaction with Alcohol

Use of oral metronidazole is associated with a disulfiram-like reaction to alcohol, including abdominal cramps, nausea, vomiting, headaches, and flushing. Discontinue consumption of alcohol or products containing propylene glycol during and for at least three days after therapy with metronidazole (see **PRECAUTIONS-Drug Interactions**).

Cockayne Syndrome

Metronidazole Injection is contraindicated in patients with Cockayne syndrome. Severe irreversible hepatotoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole in patients with Cockayne syndrome (see **ADVERSE REACTIONS**).

WARNINGS

Hypersensitivity Reactions

Hypersensitivity reactions including toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with the use of metronidazole. Symptoms can be serious and potentially life threatening (see **ADVERSE REACTIONS**)

Central and Peripheral Nervous System Effects

Encephalopathy and peripheral neuropathy: Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.

Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.

Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity.

Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis: Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

The appearance of abnormal neurologic signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy (see **ADVERSE REACTIONS**).

PRECAUTIONS

General

Hepatic Impairment

Patients with hepatic impairment metabolize metronidazole slowly, with resultant accumulation of metronidazole in the plasma. For patients with severe hepatic impairment (Child-Pugh C), a reduced dose of Metronidazole Injection, USP is recommended. For patients with mild to moderate hepatic impairment, no dosage adjustment is needed but these patients should be monitored for metronidazole associated adverse events (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Patients with end-stage renal disease may excrete metronidazole and metabolites slowly in the urine, resulting in significant accumulation of metronidazole metabolites. Monitoring for metronidazole associated adverse events is recommended (see **CLINICAL PHARMACOLOGY**).

Fungal Superinfections

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candicidal agent.

Use in Patients with Blood Dyscrasias

Metronidazole is a nitromidazole, and should be used with care in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies.

Monitoring for Leukopenia

Total and differential leukocyte counts are recommended before, during, and after prolonged or repeated courses of metronidazole therapy.

Sodium Retention

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering metronidazole injection to patients receiving corticosteroids or to patients predisposed to edema.

Drug-Resistant Bacteria

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial

infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Interaction with Alcohol

Discontinue consumption of alcoholic beverages or products containing propylene glycol while taking Metronidazole Injection, USP and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur (see **CONTRAINDICATIONS**, **PRECAUTIONS-Drug Interactions**).

Treatment of Bacterial Infections

Patients should be counseled that antibacterial drugs including Metronidazole Injection, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Metronidazole Injection, USP is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Metronidazole Injection, USP or other antibacterial drugs in the future.

Drug Interactions

Disulfiram

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks (see **CONTRAINDICATIONS**).

Alcoholic Beverages

Abdominal cramps, nausea, vomiting, headaches and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following metronidazole therapy (see **CONTRAINDICATIONS**).

Warfarin and other Oral Anticoagulants

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. When metronidazole is prescribed for patients on this type of anticoagulant therapy, Prothrombin time and INR should be carefully monitored.

Lithium

In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Busulfan

Metronidazole has been reported to increase plasma concentrations of busulfan, which can result in an increased risk for serious busulfan toxicity. Metronidazole should not be administered concomitantly with busulfan unless the benefit outweighs the risk. If no therapeutic alternatives to metronidazole are available, and concomitant administration with busulfan is medically needed, frequent monitoring of busulfan plasma concentration should be performed and the busulfan dose should be adjusted accordingly.

Drugs that Inhibit CYP450 Enzymes

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

Drugs that Induce CYP450 Enzymes

The simultaneous administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

Drugs that Prolong the QT interval

QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

Drug/Laboratory Test Interactions

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotine adenine dinucleotide ($NAD^+ \rightleftarrows NADH$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tumors affecting the liver, lung, mammary and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters.

Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). Malignant tumors were increased in male mice treated at approximately 1500 mg/m^2 (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice. Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in *in vitro* assay systems including the Ames test. Studies in mammals *in vivo* have failed to demonstrate a potential for genetic damage.

Metronidazole failed to produce any adverse effects on fertility or testicular function in male rats at doses up to 400 mg/kg/day (approximately 2 times the maximum recommended daily dose based on body surface area comparison) for 28 days. However, rats treated at the same dose for 6 weeks, or longer were infertile and showed severe degeneration of the seminiferous epithelium in the testes as well as marked decreases in testicular spermatid counts and epididymal sperm counts. Fertility was restored in most rats after an eight week, drug-free recovery period.

Fertility studies have been performed in male mice at doses up to six times the maximum recommended human dose based on mg/m^2 and have revealed no evidence of impaired fertility. However, metronidazole was associated with reversible adverse effects on the male reproductive system (significantly decreased testes and epididymides weight, decreased sperm viability, and increased the incidence of abnormal sperm).

Pregnancy

Teratogenic effects

There are no adequate and well-controlled studies of Metronidazole Injection, USP in pregnant women. There are published data from case-control studies, cohort studies, and 2 meta-analyses that include more than 5,000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole *in utero*; however, these findings were not confirmed. In addition, more than ten randomized, placebo-controlled clinical trials enrolled more than 5,000 pregnant women to assess the use of antibiotic treatment (including

metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.

Metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known. Reproduction studies have been performed in rats, rabbits and mice at doses similar to the maximum recommended daily dose based on body surface area comparisons. There was no evidence of harm to the fetus due to metronidazole.

Nursing Mothers

Metronidazole is present in human milk at concentrations similar to maternal serum levels, and infant serum levels can be close to or comparable to infant therapeutic levels. Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of metronidazole therapy, and for 24 hours after therapy ends and feed her infant stored human milk or formula.

Geriatric Use

In geriatric patients, monitoring for metronidazole associated adverse events is recommended (see **CLINICAL PHARMACOLOGY**, **PRECAUTIONS**). Decreased liver function in geriatric patients can result in increased concentrations of metronidazole that may necessitate adjustment of metronidazole dosage (see **DOSAGE AND ADMINISTRATION**).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following reactions have been reported during treatment with metronidazole injection:

Central Nervous System

The most serious adverse reactions reported in patients treated with metronidazole injection have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported headache, syncope, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia (see **WARNINGS**).

The following reactions have also been reported during treatment with metronidazole injection:

Gastrointestinal

The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia and occasionally vomiting, diarrhea; epigastric distress; abdominal cramping; and constipation.

Mouth

A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which

may occur during effective therapy.

Dermatologic

Dermatitis bullous, fixed drug eruption, erythematous rash and pruritus.

Hematopoietic

Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Local Reactions

Thrombophlebitis after intravenous infusion. This reaction can be minimized or avoided by avoiding prolonged use of indwelling intravenous catheters.

Cardiovascular

QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval. Flattening of the T-wave may be seen in electrocardiographic tracings.

Hypersensitivity

Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal

Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Hepatic

Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (latency from drug start to signs of liver failure as short as 2 days) (see **CONTRAINDICATIONS**).

Other

Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported.

Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for Metronidazole Injection, USP.

OVERDOSAGE

Use of dosages of intravenous metronidazole hydrochloride higher than those recommended has been reported. These include the use of 27 mg/kg three times a day for 20 days, and the use of 75 mg/kg as a single loading dose followed by 7.5 mg/kg maintenance doses. No adverse reactions were reported in either of the two cases.

Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported included nausea, vomiting, and ataxia.

Oral metronidazole has been studied as a radiation sensitizer in the treatment of malignant tumors. Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 g every other day.

Treatment of Overdosage

There is no specific antidote for metronidazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

In elderly patients the pharmacokinetics of metronidazole may be altered and, therefore, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Treatment of Anaerobic Bacterial Infections:

The recommended dosage schedule for **Adults** is:

Loading Dose	15 mg/kg infused over one hour (approximately 1 g for a 70-kg adult).
Maintenance Dose	7.5 mg/kg infused over one hour every six hours (approximately 500 mg for a 70-kg adult). The first maintenance dose should be instituted six hours following the initiation of the loading dose.

Parenteral therapy may be changed to oral metronidazole when conditions warrant, based upon the severity of the disease and the response of the patient to treatment with Metronidazole Injection, USP treatment. The usual adult oral dosage is 7.5 mg/kg every six hours (approximately 500 mg for a 70-kg adult).

A maximum of 4 g should not be exceeded during a 24-hour period.

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

Dosage Adjustments

Patients with Severe Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), the metronidazole dose should be reduced by 50% (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS**).

Patients Undergoing Hemodialysis

Hemodialysis removes significant amounts of metronidazole and its metabolites from systemic circulation. The clearance of metronidazole will depend on the type of dialysis membrane used, the duration of the dialysis session, and other factors. If the administration of metronidazole cannot be separated from a hemodialysis session, supplementation of metronidazole dosage following a hemodialysis session should be considered, depending on the patient's clinical situation (see **CLINICAL PHARMACOLOGY**).

Prophylaxis

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

- 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery; followed by
- 7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) administration of the initial preoperative dose be completed approximately one hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) Metronidazole Injection, USP be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Metronidazole Injection, USP should be limited to the day of surgery only, following the above guidelines.

CAUTION: Metronidazole Injection, USP is to be administered by slow

intravenous drip infusion only, either as a continuous or intermittent infusion. I.V. admixtures containing metronidazole and other drugs should be avoided. Additives should not be introduced into this solution. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion. DO NOT USE EQUIPMENT CONTAINING ALUMINUM (e.g., NEEDLES, CANNULAE) THAT WOULD COME IN CONTACT WITH THE DRUG SOLUTION.

Metronidazole Injection, USP is a ready-to-use isotonic solution. NO DILUTION OR BUFFERING IS REQUIRED. Do not refrigerate. Each container of Metronidazole Injection contains 14 mEq of sodium.

Do not use if cloudy or precipitated or if the seal is not intact.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Use sterile equipment. It is recommended that the intravenous administration apparatus be replaced at least once every 24 hours.

INSTRUCTIONS FOR USE

To Open

Tear outer wrap at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

Preparation for Administration

(Use aseptic technique)

- Close flow control clamp of administration set.
- Remove cover from outlet port at bottom of container.
- Insert piercing pin of administration set into port with a twisting motion until the set is firmly seated. **NOTE:** See full directions on administration set carton.
- Suspend container from hanger.
- Squeeze and release drip chamber to establish proper fluid level in chamber.
- Open flow control clamp and clear air from set. Close clamp.
- Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
- Regulate rate of administration with flow control clamp.

WARNING: Do not use flexible container in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

HOW SUPPLIED

Metronidazole Injection, USP, sterile, is supplied in 100 mL single dose flexible containers, each containing 500 mg (5 mg/mL) of metronidazole (List 7811).

Unit of Sale	Concentration
NDC 0409-7811-37 Case of 80 100 mL single dose flexible containers	500 mg/100 mL (5 mg/mL)
NDC 0409-7811-24 Case of 24 100 mL single dose flexible containers	500 mg/100 mL (5 mg/mL)

Metronidazole Injection, USP should be stored at 20 to 25°C (68 to 77°F) [See USP Controlled Room Temperature] and protected from light during storage.

Distributed by:
Hospira, Inc., Lake Forest, IL 60045 USA

LAB-0873-8.0

Revised: 01/2023

PRINCIPAL DISPLAY PANEL - 5 mg/mL Bag Label - IM-4456

100 mL
NDC 0409-7811-31

METRONIDazole
Injection, USP
500 mg/100 mL (5 mg/mL)

EACH mL CONTAINS METRONIDAZOLE 5 mg; SODIUM CHLORIDE 7.9 mg; DIBASIC SODIUM PHOSPHATE, ANHYDROUS 0.48 mg; CITRIC ACID, ANHYDROUS 0.23 mg. SODIUM 14 mEq/100 mL. 314 mOsmol/LITER (CALC.). pH 5.8 (4.5 to 7.0).

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

DO NOT REFRIGERATE

SINGLE-DOSE CONTAINER. FOR INTRAVENOUS USE. USUAL DOSAGE: SEE INSERT. STERILE, NONPYROGENIC. PROTECT FROM LIGHT. USE ONLY IF SOLUTION IS CLEAR AND CONTAINER IS UNDAMAGED. MUST NOT BE USED IN SERIES CONNECTIONS.

RX ONLY

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LAKE FOREST,
IL 60045 USA

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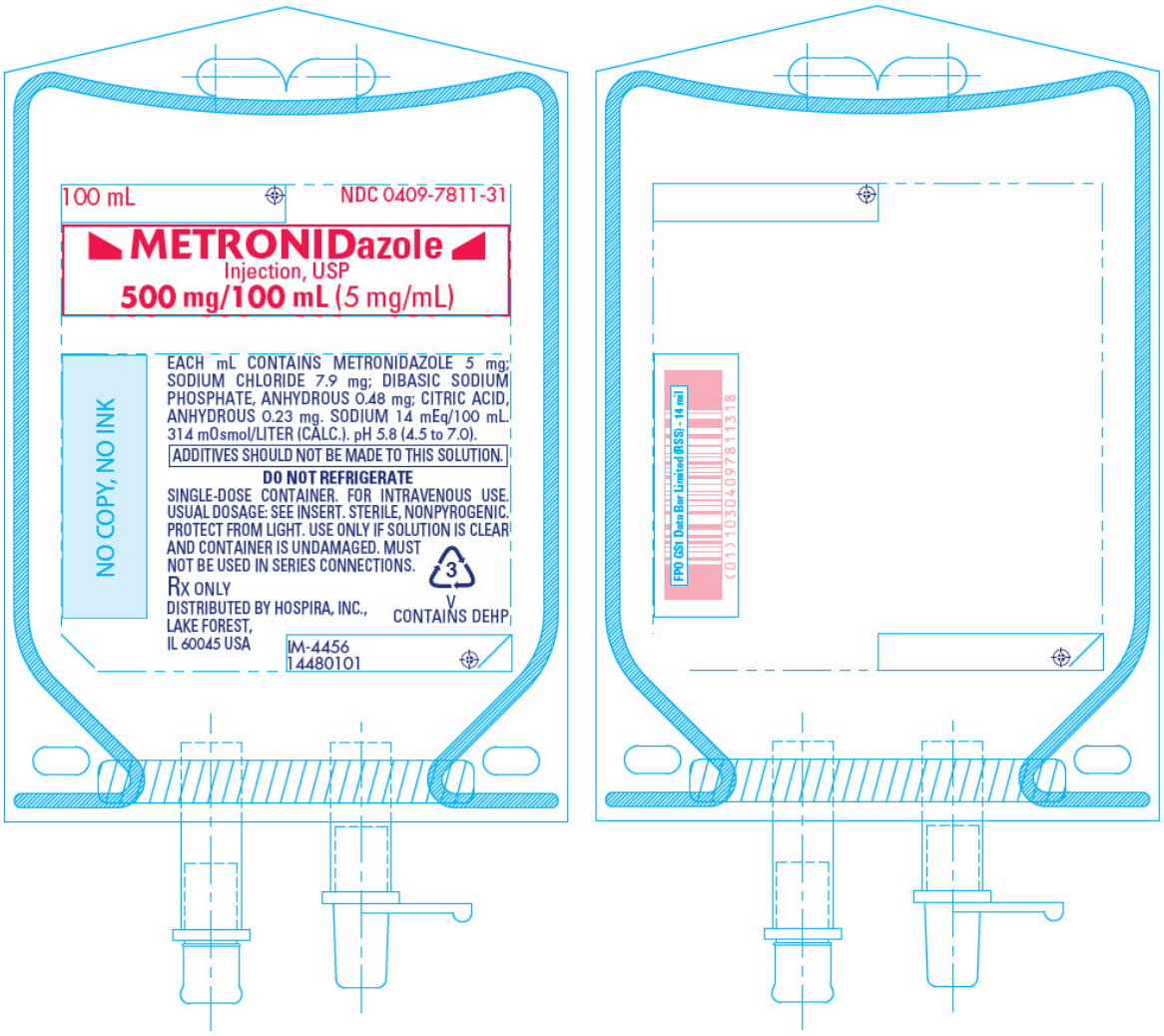
V
CONTAINS DEHP

IM-4456
14480101



PRINCIPAL DISPLAY PANEL - 5 mg/mL Bag Pouch - WR-0585

TO OPEN – TEAR AT NOTCH

NDC 0409-7811-31
One Unit

METRONIDazole
Injection, USP

Rx only

500 mg/100 mL (5 mg/mL)

Each mL contains metronidazole 5 mg; sodium chloride 7.9 mg; dibasic sodium phosphate, anhydrous 0.48 mg; citric acid, anhydrous 0.23 mg. Sodium 14 mEq/100 mL.
314 mOsmol/liter (CALC.). pH 5.8 (4.5 to 7.0).

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION

DO NOT REFRIGERATE

Single-dose container. For intravenous use. Usual dose: See insert. Sterile, nonpyrogenic.
Protect from light. Use only if solution is clear. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired. Must not be used in series connections.

The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when pouch is opened. Store at 20 to 25°C (68 to 77°F). [See

USP Controlled Room Temperature.] Protect from freezing. See insert.

F WR-0585

Hospira

Not Made With Natural Rubber Latex

14480201

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PRINCIPAL DISPLAY PANEL - 5 mg/mL Bag Label - IM-4457

100 mL
NDC 0409-7811-11

METRONIDazole
Injection, USP
500 mg/100 mL (5 mg/mL)

EACH mL CONTAINS METRONIDAZOLE 5 mg;
SODIUM CHLORIDE 7.9 mg; DIBASIC SODIUM
PHOSPHATE, ANHYDROUS 0.48 mg; CITRIC ACID,
ANHYDROUS 0.23 mg. SODIUM 14 mEq/100 mL.
314 mOsmol/LITER (CALC.). pH 5.8 (4.5 to 7.0).

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

DO NOT REFRIGERATE

SINGLE-DOSE CONTAINER. FOR INTRAVENOUS USE.
USUAL DOSAGE: SEE INSERT. STERILE, NONPYROGENIC.

PROTECT FROM LIGHT. USE ONLY IF SOLUTION IS CLEAR
AND CONTAINER IS UNDAMAGED. MUST
NOT BE USED IN SERIES CONNECTIONS.

RX ONLY

DISTRIBUTED BY HOSPIRA, INC.,
LAKE FOREST,
IL 60045 USA

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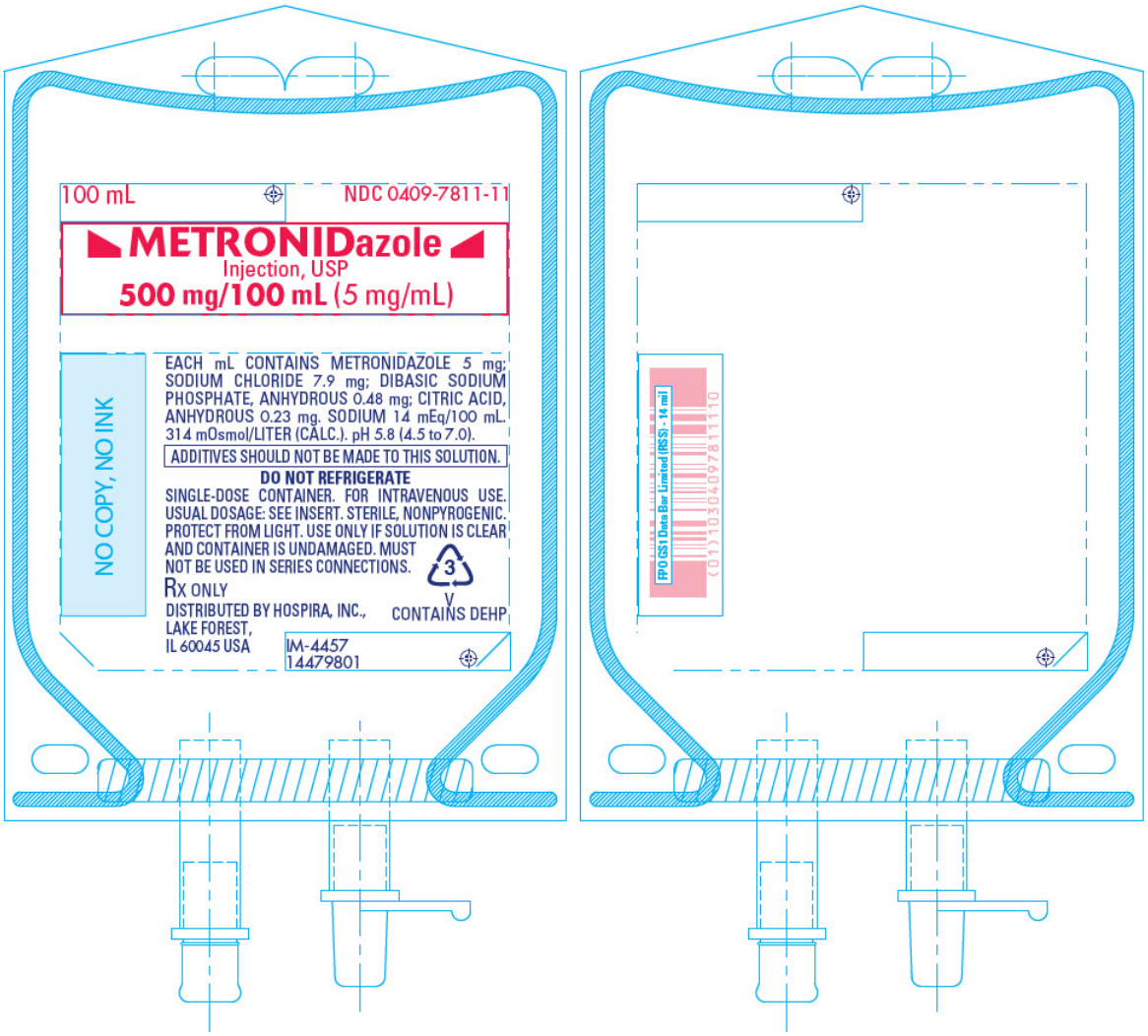
V
CONTAINS DEHP

IM-4457
14479801



PRINCIPAL DISPLAY PANEL - 5 mg/mL Bag Pouch - WR-0586

TO OPEN — TEAR AT NOTCH

NDC 0409-7811-32
Contains Four Units of NDC 0409-7811-11

METRONIDazole
Injection, USP

Rx only

500 mg/100 mL (5 mg/mL)

Each mL contains metronidazole 5 mg; sodium chloride 7.9 mg; dibasic sodium phosphate, anhydrous 0.48 mg; citric acid, anhydrous 0.23 mg. Sodium 14 mEq/100 mL.
314 mOsmol/liter (CALC.). pH 5.8 (4.5 to 7.0).

ADDITIVES SHOULD NOT BE MADE TO THIS SOLUTION.

DO NOT REFRIGERATE

Single-dose container. For intravenous use. Usual dose: See insert. Sterile, nonpyrogenic. Protect from light. Use only if solution is clear. After removing the overwrap, check for minute leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired. Must not be used in series connections.

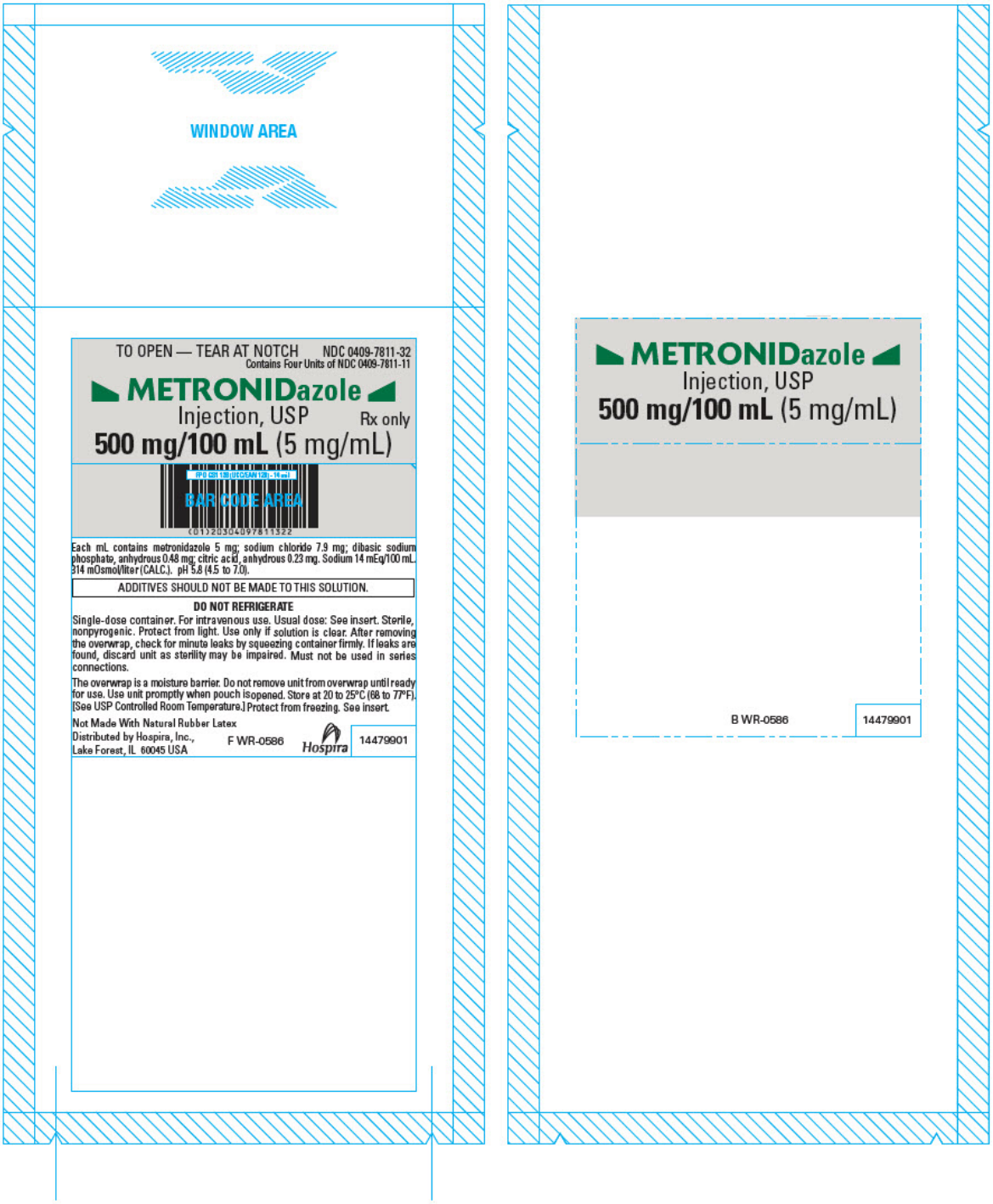
The overwrap is a moisture barrier. Do not remove unit from overwrap until ready for use. Use unit promptly when pouch is opened. Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Protect from freezing. See insert.

Not Made With Natural Rubber Latex
Distributed by Hospira, Inc.,
Lake Forest, IL 60045 USA

F WR-0586

Hospira

14479901



METRONIDAZOLE

metronidazole injection, solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:0409-7811
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METRONIDAZOLE (UNII: 140QMO216E) (METRONIDAZOLE - UNII:140QMO216E)	METRONIDAZOLE	500 mg in 100 mL

Inactive Ingredients

Ingredient Name	Strength
SODIUM CHLORIDE (UNII: 451W47IQ8X)	790 mg in 100 mL
SODIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: 22ADO53M6F)	48 mg in 100 mL
ANHYDROUS CITRIC ACID (UNII: XF417D3PSL)	23 mg in 100 mL
WATER (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0409-7811-24	24 in 1 CASE	09/07/2005	
1		1 in 1 POUCH		
1	NDC:0409-7811-31	100 mL in 1 BAG; Type 0: Not a Combination Product		
2	NDC:0409-7811-37	20 in 1 CASE	09/19/2005	
2	NDC:0409-7811-32	4 in 1 POUCH		
2	NDC:0409-7811-11	100 mL in 1 BAG; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA018890	09/07/2005	

Labeler - Hospira, Inc. (141588017)

Revised: 1/2023 Hospira, Inc.